as the invention." *See* Paper No. 11, Page 3, Paragraph 3. Specifically, the Examiner rejected claim 49 as indefinite because the term "claim 50 contiguous comprising" requires amendment. Applicants have cancelled claim 49, and accordingly assert that the Examiner's concerns have been rendered moot.

The Examiner rejected claims 23, 25, 27, 29, 31, 33, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 61, 65, 67, 69, 71, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, and 96 under 35 U.S.C. § 112, second paragraph, as allegedly "being of improper dependent form for failing to further limit the subject matter of a previous claim." *See* Paper No. 11, Page 3, Paragraph 4. Specifically, the Examiner alleges that the term "heterologous" does not further limit these dependent claims.

Applicant's respectfully disagree and traverse this rejection.

The independent claims from which these rejected claims depend (e.g., claim 21) encompass polypeptides comprising the specified region of SEQ ID NO:2 either with, or without, a heterologous polypeptide. The rejected claims (e.g., claim 23) merely specify that the polypeptide includes a heterologous polypeptide. Thus, the claims very clearly provide a further limitation of the subject matter of the claims from which they depend. Therefore, Applicants respectfully request that the rejection under § 112, second paragraph with respect to "heterologous" be withdrawn.

Rejections Under 35 U.S.C. § 101

The Examiner rejected claims 21-96 under 35 U.S.C. § 101 as allegedly unsupported by either a specific and substantial asserted utility or a well established utility. *See* Paper No. 11, Pages 3-4.

Applicants respectfully disagree and traverse this rejection.

A rejection under 35 U.S.C. § 101 is improper when a person of ordinary skill in the art would find credible disclosed features or characteristics of the invention, or statements made by the applicant in the written description of the invention. *See* M.P.E.P. §§ 2107.01(II), (III) at 2100-[29-31] (Rev. 1, Feb. 2000). In addition, an applicant need only make *one* credible assertion of utility for the claimed invention to satisfy 35 U.S.C. § 101. *See, e.g., Raytheon v. Roper,* 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). *See* M.P.E.P. at 2100-29. Finding a lack of utility is also

improper if a person of ordinary skill in the art would know of a use for the claimed invention at the time the application was filed. M.P.E.P. § 2107.01(II)(B) at 2100-[29-30].

Moreover, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility. M.P.E.P. § 2107.01(II)(A) at 2100-[31-32]. Thus, the Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *Id.* The Examiner must also present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicants' assertion of utility. *See id.*; *see also, In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

Contrary to the Examiner's comments, Applicants have set forth in the specification statements that clearly describe a function of Connective Tissue Growth Factor-2 ("CTGF-2") polypeptides and fragments and explain why the invention is useful. The specification, at page 28, first full paragraph extending to page 29; page 18, third full paragraph; and page 19, second full paragraph, for example, teaches that CTGF-2 polypeptides of the invention may be employed to raise antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth. Applicants assert that such characterization is sufficient on its own to constitute a showing of utility.

Other than the conclusory statements that the invention lacks utility, the Examiner has presented no arguments as to why this asserted utility is not credible. In arguing that Applicants' asserted utility is not credible, the Examiner must attack (a) the logic underlying the assertion as seriously flawed or (b) the facts upon which the assertion is based as inconsistent with the logic underlying the assertion. *See* Revised Interim Utility Guidelines Training Materials, p. 5. In the instant rejection, the Examiner has set forth no arguments as to why Applicants' logic (that CTGF-2 polypeptide fragments have the utility of raising antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth) is flawed or that the facts upon which the logic is based on, are inconsistent with the underlying assertion. Thus, the Examiner has failed to make even a *prima facie* showing that Applicants' asserted utility is not credible.

Moreover, Applicants respectfully submit that CTGF-2 polypeptide fragments of the invention have an immediate and specific utility. Such polypeptides may be used to raise

antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth. *See, e.g.*, specification, at page 28, first full paragraph extending to page 29; page 18, third full paragraph; and page 19, second full paragraph. Thus, polypeptides of the invention are supported by an immediate utility that is both specific and substantial.

Applicants submit that these asserted utilities for CTGF-2 are specific (not every polypeptide fragment has a utility of raising antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, Applicants submit that these utilities are credible. The Examiner has failed, however, to provide any countervailing statements as to why these particular utilities are not specific, substantial and credible.

Even assuming, *arguendo,* the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one skilled in the art to conclude that the asserted utilities are more likely than not true. Applicants have directed the Examiner to the specification where clear and specific assertions are made of CTGF-2 polypeptide fragment utilities.

Furthermore, applicants submit that the asserted utility (i.e., CTGF-2 polypeptides may be used to raise antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth) is well supported by the art. CTGF-2, also known in the art as "Cyr61", has been shown by Xie et al. to be overexpressed in some breast cancer cell lines, and was also shown to induce tumor formation in normal breast cells expressing Cyr61 in nude mice. Specifically,

> Tumors from the normal breast cells expressing Cyr61 (MCF-12A/61) first became apparent 3 weeks after injection, and all of the mice developed tumors ranging from 0.6 to 1.4 g at 6 weeks after injection.... In contrast, the control mice that received MCF-12A/V cells containing empty vector remained tumor-free even at 12 weeks after injection....

(Xie, D., et al., *J. Biol. Chem.*, *276*:17 (14187-14194), (attached hereto as Exhibit A)). Accordingly, Xie, et al. confirm, as stated in the specification, that CTGF-2 polypeptides and fragments thereof have both a specific and substantial utility (i.e., CTGF-2 polypeptides may be

used to raise antibodies (e.g., antagonistic antibodies), which can be employed to prevent CTGF-2 dependent tumor growth), that is credible.

In view of the above, Applicants submit that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101. The Examiner has failed to establish and maintain grounds as to why a rejection for lack of utility is proper. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 21-96 under 35 U.S.C. § 112, first paragraph, specifically alleging that "since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility...one skilled in the art clearly would not know how to use the claimed invention." *See* Paper No. 11, Page 5.

Applicants respectfully disagree and traverse this rejection.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a credible and specific asserted utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-28. Therefore, because the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn. Thus, Applicants assert that because the claimed invention is supported by a credible and specific asserted utility, one of skill in the art would know how to use the invention for one of its intended purposes.

The Examiner rejected claims 21-96 under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description, as "containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *See* Paper No. 11, Page 6.

Applicants respectfully disagree and traverse this rejection.

As an initial matter, Applicants request clarification as to the reason claims 22 and 23 were rejected under 35 U.S.C. § 112, first paragraph. The subject matter relating to these claims was specifically described in the specification in such a way as to convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and the Examiner's comments do not appear to indicate otherwise. Accordingly,

Applicants respectfully request that the rejection of these claims for alleged lack of adequate written description be withdrawn.

The Examiner alleges that the specification and claims "do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising polypeptide fragments of SEQ ID NO:2...amino acid sequences which are heterologous to SEQ ID NO:2, nor fragments derived therefrom." *See* Paper No. 11, Page 6, Paragraph 3. The Examiner has cited *University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) (hereinafter "Eli Lilly") and *Fiers v. Revel*, 984 F.2d 1164, 1171; 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (hereinafter "Fiers") for the proposition that an applicant complies with the written description requirement through the use of descriptive structures that set forth the claimed invention, and that an adequate written description requires precise definition of a structure, formula, chemical name or physical properties. Applicants respectfully but emphatically disagree that *Eli Lilly* and *Fiers* support a written description rejection of Applicants' claims.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; 19 USPQ2d 1111, 1116 (Fed. Cir 1991); M.P.E.P. § 2163.02.

According to the court in *Eli Lilly*, a written description may be adequate if it defines "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1569. Similarly, the court in *Fiers* held that an adequate written description "requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Fiers*, 984 F.2d at 1170. In both *Fiers* and *Eli Lilly* however, the genus was described entirely by function, with no reference at all to structure. The presently claimed genus, in contrast, is entirely described by structure.

The specification as filed contains the description of the full-length CTGF-2 polypeptide sequence as SEQ ID NO:2. Applicants assert that the structural recitation of SEQ ID NO:2 constitutes a recitation of structural features common to the members of the genus, which features "constitute a substantial portion of the genus." Id. That is, the recitation of the amino acid sequence of SEQ ID NO:2 is a recitation of the structural features common to the members of the genus because each of the fragments and variants of SEQ ID NO:2 will share at least some

structural features with SEQ ID NO:2. Furthermore, the specification, for example, at page 9, first to third full paragraph, recites types of CTGF-2 fragments and variants that could be generated using the full-length CTGF-2 polypeptide sequence. Likewise, polypeptide sequences that are at least 95% homologous to the CTGF-2 sequence of SEQ ID NO:2 will share at least some structural features common to the members of the genus because the proteins included within the genus will have 95% of their amino acid sequence (primary structure) in common with the amino acid sequence of SEQ ID NO:2. Indeed, SEQ ID NO:2 alone constitutes a representative number of species of the genus, since one of skill in that art could easily visualize or recognize the identity of the members of the claimed genus based upon the teachings of the specification as filed. Moreover, Applicants note that claims 34 and 72 have been amended to specify a function for the genus of polypeptides. Thus, the skilled person would readily conclude that the inventors had possession of the claimed invention in the specification as filed. Accordingly, Applicants respectfully request that the rejection to these claims be withdrawn.

Rejections Under 35 U.S.C. 102

The Examiner rejected 21, 23, 25, 27, 30-34, 36, 38, 40, 42, 44, 46, 51-59, 61, 63, 65, 68-72, 74, 76, 78, 80, 82, 84, and 89-96 under 35 U.S.C. § 102(b) as anticipated by Purchio et al., Latinkic et al., and O'Brien et al.

Applicants have amended the pending claims, and assert that the Examiner's rejection of claims 21, 23, 25, 27, 30-34, 36, 38, 40, 42, 44, 46, 51-59, 61, 63, 65, 68-72, 74, 76, 78, 80, 82, 84, and 89-96 under 35 U.S.C. § 102(b) have been rendered moot in light of the claim amendments.

Applicants submit that for the reasons stated above, neither the disclosures of Purchio et al., Latinkic et al., and O'Brien et al., alone or in combination, teach or suggest the claimed polypeptides. Accordingly, the cited art alone or in combination, does not anticipate the claimed invention, and the rejection under 35 U.S.C. §102 (b) should be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants believe they have fully addressed the Examiner's concerns and that this application is now in condition for allowance. An early notice to that effect is urged. A request is made to the Examiner to call the undersigned at the phone

number provided below if any further action by Applicants would expedite allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: MAY 31, 2001

Jonathan L. Klein (Reg. No. 41,119)
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (301) 251-6015
Facsimile: (301) 309-8439

Enclosure
JKE/RL/lcc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: LI et al.

Application Serial No.: 09/348,815

Filed: July 8, 1999

For: Connective Tissue Growth Factor-2

Art Unit: 1635

Examiner: Zara, J.

Attorney Docket No.: PF126P1D1

VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Claims

Claims 21, 34, 59, and 72 have been amended as follows:

21. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 1 to 381 of SEQ ID NO:2;

(b) amino acids 2 to 381 of SEQ ID NO:2;

(c) amino acids 25 to 381 of SEQ ID NO:2; and

(d) a polypeptide fragment of SEQ ID NO:2, wherein said fragment stimulates cellular proliferation~~; and~~

~~(e) at least 30 contiguous amino acids of amino acids 1 to 381 of SEQ ID NO:2~~.

34. (Once Amended) An isolated polypeptide comprising a first amino acid sequence that is at least ~~90%~~ 95% identical to a second amino acid sequence selected from the group consisting of:

(a) amino acids 1 to 381 of SEQ ID NO:2;

(b) amino acids 2 to 381 of SEQ ID NO:2;

(c) amino acids 25 to 381 of SEQ ID NO:2; and

(d) a polypeptide fragment of SEQ ID NO:2;

wherein said polypeptide stimulates cellular proliferation~~; and~~

~~(e) at least 30 contiguous amino acids of amino acids 1 to 381 of SEQ ID NO:2~~.

59. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804;

(b) the amino acid sequence of the full-length polypeptide, lacking the N-terminal methionine, encoded by the human cDNA contained in ATCC Deposit Number 75804;

(c) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804; and

(d) a polypeptide fragment of the polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804, wherein said fragment stimulates cellular proliferation~~; and~~

~~(e) at least 30 contiguous amino acids of the polypeptide encoded by the human cDNA contained ATCC Deposit Number 75804~~.

72. (Once Amended) An isolated polypeptide comprising a first amino acid sequence that is at least ~~90%~~ 95% identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804;

(b) the amino acid sequence of the full-length polypeptide, lacking the N-terminal methionine, encoded by the human cDNA contained in ATCC Deposit Number 75804;

(c) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804; and

(d) a polypeptide fragment of the polypeptide encoded by the human cDNA contained in ATCC Deposit Number 75804;

wherein said polypeptide stimulates cellular proliferation~~; and~~

~~(e) at least 30 contiguous amino acids of the polypeptide encoded by the human cDNA contained ATCC Deposit Number 75804~~.